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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Cancer Treatment and Metastasis Prevention

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(57) 16 Claims

ABSTRACT

A new method for the treatment of cancer in a human particularly malignant tumours, for example those in a breast or breasts, said method comprising the steps of:

(1) directly injecting into the tumour a dosage amount of a pharmaceutical composition comprising an effective amount of an anti-cancer drug and/or drug suitable for use to treat cancer (for example about 1 to about 2 mg Novantrone [tm] (Mitoxantrone), other chemotherapeutic agent, NSAIDs) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water, and

(2) administering systemically, preferably intravenously, a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid/or pharmaceutically acceptable and salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce the side effects of any medicine (for example NSAID) administered therewith if the amount of the form of hyaluronic acid exceeds about 200 mg/70kg person)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark

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Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol);

(b) an anti-cancer drug, and

(c) a drug suitable for use to treat cancer

and combinations thereof

optionally together with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

TITLE OF INVENTION

CANCER TREATMENT AND METASTASIS PREVENTION

FIELD OF INVENTION

This invention relates to the treatment of cancer and the prevention of metastases in patients having cancer. This invention also relates to pharmaceutical compositions and dosage amounts suitable for such treatment and prevention. In one application this invention relates to the treatment of breast cancer and the prevention of metastases in a patient with breast cancer.

BACKGROUND OF THE INVENTION

Conventional treatment of breast cancer involves a mastectomy, the surgical removal of breast tissue. The procedure can vary from a simple lumpectomy to the radical procedure during which the surgeon removes the internal mammary chain of lymph nodes, the underlying pectoral muscles and the adjacent axillary lymph nodes.

In the instances of early detection of cancers of the breast, breast conserving therapy is now considered appropriate. Thus, lumpectomy together with axillary clearance and radiotherapy are presently recommended as alternatives. However, there is still considerable controversy surrounding the ultimate minimum treatment to achieve adequate local control. This is true with all cancers. In the considerations therefore, the choice of treatment will be made to eliminate the cancer and ensure no recurrence, for example in the breast or elsewhere by metastases.

Published application WO91/04058 provides a new treatment for among other diseases, cancer providing for administration of dosage amounts of pharmaceutical compositions comprising effective amounts of each of NSAIDs, Vitamin C, anti-cancer agents, among other medicines and therapeutic agents with a form of hyaluronic acid, for example sodium hyaluronate having a molecular weight less than 750,000 daltons, in an amount equal to or exceeding 10 mg/70 kg person. At page 27, line 35 the document provides that the doses can be

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administered intravenously, intra-arterially, intraperitoneally, intra-pleurally and directly into the tumour by injection through a needle placed under sonograph or CT guidance.

Case VII found at page 42-43 discloses the treatment of massive cancer of the breast with supraclavicular and auxiliary lymph nodes palpable. The treatment involved combinations "of hyaluronic acid and/or salts thereof added to conventional chemotherapy used systemically by injection into the tumour and by intra-pleural cavity instillation" (page 45, lines 3-5).

The said document also teaches the systemic administration of combinations of hyaluronic acid and/or salts thereof with NSAIDs (non-steroidal anti-inflammatory drug), ascorbic acid (Vitamin C), anti-cancer drugs among other drugs.

Puhlication WO/CA93/00061 relates to the topical treatment of skin diseases and conditions and involves the topical administration of specified dosage amounts of pharmaceutical compositions taught. Basal cell carcinoma, for example is treated and resolved by such topical administration. The dosage amounts when discharged from the skin, unload into the lymphatic system (page 31, line 35). During their stay in the skin, particularly the epidermis, the drugs treat the disease or condition in the skin with the form of hyaluronic acid (for example sodium hyaluronate having a molecular weight less than 750,000 daltons) transporting the drugs into the skin. Where an NSAID is used, synthesis of prostaglandin is inhibited, deblocking the macrophages and N.K. cells (page 26, line 27 to page 27, line 35) thereby permitting the macrophages and N.K. cells to destroy the disease or condition.

While the destruction/clearance of the malignant tumour and all cancer present is the end goal, it cannot be undertaken without concern for metastatic effects. Metastases and recurrence must be prevented particularly metastases into vulnerable organs such as the liver.

In the past treatments, not enough emphasis and concern was placed on the metastatic effect (metastases). Focus was on destruction and clearing. Thus, in the treatments prescribed or undertaken in the past, attempts were made to destroy the malignant tumour. However, prostaglandin synthesis in many approaches was permitted in the tissue (inhibiting the macrophages and N. K. cells from performing their function (killing cancer cells and destruction of the tumour)). Therefore cancer cells freed from the tumour instead of being destroyed, were permitted to travel in the body and lodge in a more vulnerable area (the liver or lungs, for example) - a certain recipe for metastases.

It is therefore an object of this invention to provide a new treatment for cancer which finds one particular application in the treatment of breast cancer.

It is a further object of this invention to reduce the risk of metastases with such treatment.

It is still a further object of the invention to reduce the risk of the recurrence of the disease, for example breast cancer.

It is still a further object of the invention to provide pharmaceutical compositions and dosage amounts of pharmaceutical compositions suitable for use in such treatments.

Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments.

SUMMARY OF THE INVENTION

Unexpectedly, Applicants have discovered a new treatment for cancer (for example breast cancer - malignant tumours of the breast) which not only causes the malignant tumours (such as those of the breast) to shrink, recede and disappear, but also unexpectedly reduces the risk of metastases.

According to one aspect of the invention, Applicants have provided a new method for the treatment cancer in a human particularly malignant

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tumours, for example those in a breast or breasts, said method comprising the steps of:

(1) directly injecting into the tumour a non-toxic dosage amount of a pharmaceutical composition comprising an effective non-toxic amount of an anti-cancer drug and/or drug suitable for use to treat cancer (for example about 1 to about 2 mg Novantrone [tm] (Mitoxantrone) or other chemotherapeutic agent, (interferon or an NSAID) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water. (The size of the tumour will limit the amount that can be directly injected into the tumour.), and

(2) administering preferably systemically (preferably intravenously) a combination, preferably a dosage amount of a pharmaceutical composition, comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce the side effects of any medicine (for

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example NSAID) administered therewith if the amount of the form of hyaluronic acid exceeds about 200mg/70kg person)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an effective non-toxic amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol);

(b) an effective nontoxic amount of a chemotherapeutic agent as described in (1) above (an anti-cancer drug, or drug suitable to treat cancer, etc.)

and combinations thereof,

optionally with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

Where more than 200mg/70kg person of the form of hyaluronic acid is used, adverse side effects of administering the drug (NSAID, chemotherapeutic agent) are reduced if not eliminated.

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The frequency of treatment for malignant tumours generally can be one (1) to four (4) times monthly or more (as may be required). For breast cancers, the frequency of the direct injections into the malignant tumour in the breast of pharmaceutical compositions of subparagraph (i) above and systemic (intravenous) administration of a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg of the drug administered with the form of hyaluronic acid with the amounts of the form of hyaluronic acid exceeding 200mg/70kg person or more (because of a lack of toxicity)

(ii) a drug selected from the group comprising a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark

Voltarol); and

(b) an effective non-toxic amount of a chemotherapeutic agent as described in (1) above (an anti-cancer drug, or drug suitable to treat cancer, etc.)

and combinations thereof,

optionally with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C) is about one (1) to three (3) times per month. (The form of hyaluronic acid, for example sodium hyaluronate, transports (causes the transport) of the medicines and therapeutic agents into the tumour tissue for their destruction and inhibits prostaglandin synthesis.)

Hyperthermia (heat) treatments may be applied to the breast having the malignant tumour. Other regimens of therapeutic treatment may also be given. For example as a precaution, depending on the amount of NSAID administered and amount of sodium hyaluronate administered, an ulcerative medicine such as Ranitidine may also be administered intravenously with sodium hyaluronate.

In accordance with another aspect of the invention, Applicants have provided a new method for the treatment of cancer, said method comprising the steps of

(1) administering systemically (preferably intravenously) to a human, a dosage amount comprising an effective non-toxic amount of a drug suitable for treating cancer, alone or preferably with an effective amount of a form of hyaluronic acid, for example,

hyaluronic acid or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight of less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) and

(2) administering systemically (preferably intravenously) a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol);

(b) an effective non-toxic dosage amount of a chemotherapeutic agent for treating cancer

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and combinations thereof,

preferably with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

The steps are repeated over a period of time at chosen intervals suitable for the patient.

Unexpectedly and in accordance with another aspect of the invention, patients regularly administered dosage amounts described above over their period of treatment, did not experience any metastatic effect (did not have any metastasis). Thus, their risk of metastases dramatically and surprisingly decreased substantially.

Thus, in accordance with another aspect of the invention, Applicants have provided a new treatment for the reduction of the risk of a patient suffering from a cancer of having the cancer metastasize (reduce the risk of such patient suffering from a metastasis or suffering from a metastatic effect), said treatment comprising (preferably with other treatment for cancer for example those described above) administering systemically (preferably intravenously) a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of

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toxicity)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an effective non-toxic amount of from for example about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol); and

(b) an effective non-toxic dosage amount of a chemotherapeutic agent (an anti-cancer agent or a drug suitable to treat cancer and combinations thereof, preferably with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C),

said administration continuing at regular intervals (for example 1 - 4 times monthly) over the period the treatment is being administered to the patient for the treatment of the cancer.

Applicants believe that the above treatments are successful because prostaglandin synthesis is inhibited thereby reactivating the macrophages and N.K. cells to destroy the cancer, neoangiogenesis is prevented, or at least precluded (by the combination of HA/NSAIDs), prostacyclin production is

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enhanced by the Vitamin C (sodium ascorbate) where used, and the hyaluronic acid (for example sodium hyaluronate) is cleared through the lymphatic system (by direct measurement the concentration of hyaluronan (occurring in the body) is 10 times higher in the lymph than the plasma. We have also observed a prolonged effect after only a simple dose of medicine with HA (form of hyaluronic acid, for example sodium hyaluronate) which is, Applicants believe due to the fact that HA administered intravenously will track through the lymphatics. One would therefore anticipate an improved and prolonged effect in terms of immunosuppression for example with cyclosporin. This has been confirmed in some initial experiments using intestinal allograft transplants in which the bowel is transplanted on an arterial venous pedicle but has all the lymphatics stripped off. Thus, when the drug enters through the arterial circulation it tracks into the lymphatics but there is no lymphatic drainage by which to exit from the bowel. The drug therefore remains in the grafts for a long period. In our initial experiments one and two doses of cyclosporin in HA produced indefinite survival of the allograft).

Because the for example sodium hyaluronate transports, carries and causes the transport of the drug, the drug is also carried to and liberated in the lymph nodes. Because the blood stream will also take up for example the sodium hyaluronate and thus the drug, the sodium hyaluronate and drug will be delivered to the liver (with the sodium hyaluronate transporting the drug into the tissue and cells of the liver). Thus, two major sites of nascent metastasis have for example sodium hyaluronate and drug (for example NSAID, anti-cancer drug) delivered to them with the sodium hyaluronate facilitating the transport of drug into the tissue (of the lymph nodes and liver) wherein to prevent cancer development and/or metastasis. Thus, the sodium hyaluronate (and other forms of hyaluronic acid, including hyaluronic acid) can be administered systemically with a drug and such administration delivers the drug with the form of hyaluronic acid to the lymph nodes and liver. Such administration helps to

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reduce the risk of metastasis and appears as a result of Applicant's tests to inhibit and even prevent metastasis of the cancer being treated in a human. Such administration may also be used to treat cancers in the lymph system and liver if cancer is found to be present there.

Where the cancer being treated is malignant tumours of the breast, and the treatment involves systemic administration, the direct injection (a number of times a month over the period of cancer treatment) of for example sodium hyaluronate with an anti-cancer drug and/or NSAID, the tumours reduced in size and cleared. Unexpectedly the reduction was without metastases.

Therefore, in accordance with another aspect of the invention, Applicants have provided new dosage amounts of pharmaceutical compositions in a form for systemic administration (usually intravenous administration from an IV bag), each such dosage amount comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity and to reduce side effects of the medicine administered with the form of hyaluronic acid where the form of hyaluronic acid exceeds about 200mg/70kg person

(ii) a drug selected from the group

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comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an effective non-toxic amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol), and

(b) an effective non-toxic dosage amount of a chemotherapeutic agent (an anti-cancer agent or a drug suitable to treat cancer and combinations thereof, preferably with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

In accordance with another aspect of the invention, Applicants have provided new dosage amounts of a pharmaceutical composition for injection (in a suitable form for injection) suitable for use with for example the above dosage amount, said dosage amount being in the container or vial suitable for use for injection (for example in a syringe) and comprising an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer (for example breast cancer, in which event the dosage amount is injected into each tumour of the breast) (for example about 1 to about 2 mg of Mitoxantrone) and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water.

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Therefore Applicants have provided the use of a new dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

(ii) an effective non-toxic amount of a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol); and an effective non-toxic amount of a chemotherapeutic agent (anti-cancer agent or an agent suitable to treat cancer)

and combinations thereof and preferably with

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25

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gm of Vitamin C) for

(a) the treatment of cancer in a patient, and (b) the prevention of metastasis in a patient suffering from cancer.

Furthermore Applicants have provided the use of

(A) a dosage amount of a pharmaceutical composition for injection (in a suitable form for injection), said dosage amount being in the container or vial for injection and comprising an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer (for example breast cancer, in which event the dosage amount is to be injected into each tumour of the breast) (for example about 1 to about 2 mg of Mitoxantrone and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water; and

(B) a dosage amount comprising

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

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(ii) an effective non-toxic amount of a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol) and

(b) an effective non-toxic amount of a chemotherapeutic agent (anti-cancer agent or an agent suitable to treat cancer);

and combinations thereof, preferably with;

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

(a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from cancer and/or

(c) delivery of the drug to the lymph system and/or liver.

Applicants have further provided the use of each of (I) non-toxic dosage amounts of a pharmaceutical composition for injection (in a suitable form for injection), said dosage amount being in the container or vial for injection and comprising an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer (for example breast cancer, in which event the dosage amount is injected into each tumour of the breast) (for example about 1 to about 2

mg of Mitoxantrone and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water and

(II) a non-toxic dosage amount comprising

(i) an effectivc amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol) and

(b) a therapeutically effective non-toxic dosage

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amount of a chemotherapeutic agent (anti-cancer agent or an agent to treat cancer) and combinations thereof, optionally with preferably

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C)

for (a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from cancer and/or

(c) delivery of a drug to the lymph system and/or liver.

Applicants have also provided each of

(A) an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to treat cancer (for example breast cancer, in which event the dosage amount is injected into each tumour of the breast) (for example about 1 to about 2 mg of Mitoxantrone and an effective amount of a form of hyaluronic acid, for example hyaluronic acid and/or pharmaceutically acceptable salts thereof, preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) (for example about 10 to about 20 mg sodium hyaluronate) in sterile water and

(B)

(i) an effective amount of a form of hyaluronic acid (for example hyaluronic acid and/or pharmaceutically acceptable salts

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thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons (for example 150,000 - 225,000 daltons) for example about 100 - 200 mg or more (because of a lack of toxicity)

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID) for example in an amount of from about 30 mg to about 100 mg (for example 30 to 60 mg of tromethamine salt of ketoralac (sold under the trade mark Toradol) and 50 to 100 mg of diclofenac or diclofenac sodium (for example sold under the trade mark Voltarol); and

(b) an effective non-toxic dosage amount of a chemotherapeutic agent (for example an anti-cancer agent or an agent to treat cancer)

and combinations thereof; with preferably

(iii) an anti-oxidant for example Vitamin C (in one embodiment 25 gm of Vitamin C).

for the manufacture of two pharmaceutical compositions, one from the components of (A) and one from the components of (B), each

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for the treatment of cancer, prevention of metastases and/or delivery of a drug to the lymph system and/or liver.

Suitable forms of sodium hyaluronate may include a fraction supplied by Hyal Pharmaceutical Corporation supplied in a 15 ml vial of sodium hyaluronate 20mg/ml (300mg/vial - Lot 2F3). The sodium hyaluronate fraction is a 2% solution with a mean average molecular weight of about 225,000 daltons. The fraction also contains water q.s. which is triple distilled and sterile in accordance with the U.S.P. for injection formulations. The vials of hyaluronic acid and/or salts thereof may be carried in a Type 1 borosilicate glass vial closed by a butyl stopper which does not react with the contents of the vial. The fraction of hyaluronic acid and/or salts thereof (for example sodium salt) and homologues, analogues, derivatives, complexes, esters, fragments, and sub-units of hyaluronic acid, preferably hyaluronic acid and salts thereof,

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may comprise hyaluronic acid and/or salts thereof having the following characteristics:

a purified, substantially pyrogen-free fraction of hyaluronic acid obtained from a natural source having at least one characteristic selected from the group (and preferably all characteristics) consisting of the following:

i) a molecular weight within the range of 150,000-225,000 daltons;

ii) less than about 1.25% sulphated mucopoly-saccharides on a total weight basis;

iii) less than about 0.6% protein on a total weight basis;

iv) less than about 150 ppm iron on a total weight basis;

v) less than about 15 ppm lead on a total weight basis;

vi) less than 0.0025% glucosamine;

vii) less than 0.025% glucuronic acid;

viii) less than 0.025% N-acetylglucosamine;

ix) less than 0.0025% amino acids;

x) a UV extinction coefficient at 257 nm of less than about 0.275;

xi) a UV extinction coefficient at 280

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nm of less than about 0.25; and

xii) a pH within the range of 7.3-7.9.

Preferably, the hyaluronic acid is mixed with water and the fraction of hyaluronic acid has a mean average molecular weight within the range of 150,000-225,000. More preferably, the fraction of hyaluronic acid may comprise at least one characteristic selected from the group (and preferably all characteristics) consisting of the following characteristics:

i) less than about 1% sulphated mucopolysaccharides on a total weight basis;

ii) less than about 0.4% protein on a total weight basis;

iii) less than about 100 ppm iron on a total weight basis;

iv) less than about 10 ppm lead on a total weight basis;

v) less than 0.00166% glucosamine;

vi) less than 0.0166% glucuronic acid;

vii) less than 0.0166% N-acetylglucosamine;

viii) less than 0.00166% amino acids;

x) a UV extinction coefficient at 257 nm of less than about 0.23;

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xi) a UV extinction coefficient at 280 nm of less than 0.19; and

xii) a pH within the range of 7.5-7.7

Applicants also propose to use sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc., having the following specifications:

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Characteristics	Specification
Appearance	White to cream colored particles
Odor	No perceptible odor
Viscosity Average Molecular Weight	< 750,000 Daltons
UV/Vis Scan, 190-820nm	Matches reference scan
OD, 260nm	< 0.25 OD units
Hyaluronidase Sensitivity	Positive response
IR Scan	Matches reference
pH, 10mg/g solution	6.2 - 7.8
Water	8% maximum
Protein	< 0.3 mcg/mg NaHy
Acetate	< 10.0 mcg/mg NaHy

Heavy Metals, maximum ppm

As	Cd	Cr	Co	Cu	Fe	Pb	Hg	Ni
2.0	5.0	5.0	10.0	10.0	25.0	10.0	10.0	5.0

Microbial Bioburden	None observed
Endotoxin	< 0.07EU/mg NaHy
Biological Safety Testing	Passes Rabbit Ocular Toxicity Test

Another form of sodium hyaluronate is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

Specifications' Test Results	
Lot No.	HG1004
pH	6.12
Condroitin Sulfate	not detected

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Protein	0.05%
Heavy Metals	Not more than 20 ppm
Arsenic	Not more than 2 ppm
Loss on Drying	2.07%
Residue on Ignition	16.69%
Intrinsic Viscosity	12.75 dl/s (XW: 679,000)
Nitrogen	3.14%
Assay	104.1%
Microbiological Counts	80/g
E. coli	Negative
Mold and Yeast	Not more than 50/g

Other forms of hyaluronic acid and/or its salts, and analogues, homologues, derivatives, complexes, esters, fragments and sub units of hyaluronic acid may be chosen from other suppliers, for example those described in prior art documents provided the form of hyaluronic acid chosen is suitable for transport of the medicine.

The following references teach hyaluronic acid, sources thereof, and processes for the manufacture and recovery thereof which may prove to be suitable.

United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

"(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 cm^3/g., and preferably greater than about 2000 cm^3/g.;

(b) a protein content of less than 0.5% by weight;

(c) ultraviolet light absorbance of a 1% solution of sodium hyaluronate of less than 3.0 at 257

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nanometers wavelength and less than 2.0 at 280 nanometers wavelength;

(d) a kinematic viscosity of a 1% solution of sodium hyaluronate in physiological buffer greater than about 1000 centistokes, preferably greater than 10,000 centistokes;

(e) a molar optical rotation of a 0.1 - 0.2% sodium hyaluronate solution in physiological buffer of less than -11 X 10^3 degree - cm^2/mole (of disaccharide) measured at 220 nanometers;

(f) no significant cellular infiltration of the vitreous and anterior chamber, no flare in the aqueous humour, no haze or flare in the vitreous, and no pathological changes to the cornea, lens, iris, retina, and choroid of the owl monkey eye when one milliliter of a 1% solution of sodium hyaluronate dissolved in physiological buffer is implanted in the vitreous replacing approximately one-half the existing liquid vitreous, said HUA being

(g) sterile and pyrogen free and

(h) non-antigenic."

Canadian Letters Patent 1,205,031 (which refers to United States Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to 730,000 and discusses processes of their manufacture.

The invention will now be illustrated with reference to the following data relating to persons suffering from cancer. A schedule of the dosage amounts received by each patient is attached and refers to the letter used

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to identify the patient. The chronology of the administration of the dosage amounts in each Schedule is in reverse order with the dosage given earliest being at the end of the Schedule and the most recent dosage being at the beginning of the Schedule.

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PATIENTS TREATED

EXAMPLE 1

Patient A - aged 42 (Female)

- breast cancer occupying the entire breast, no previous treatment
- treated with NSAIDs, sodium ascorbate, HA intravenously plus systemic therapy
- also injected with Novantrone/HA on 4 occasions
- complete response with total regression of local tumour, has not developed any metastases
- see Schedule A for dosages (HA = sodium hyaluronate having molecular weight less than 750,000 daltons)

EXAMPLE 2

Patient B - aged 60 (Female)

- local recurrence after a regional excision
- treated by direct injection with Novantrone/HA 1 mg plus 10 mgs of HA at 4 different times
- also received NSAIDs/HA intravenously
- her tumour has regressed 75% of its original size over 1.5 years
- has not developed any metastases
- see Schedule B for dosages

EXAMPLE 3

Patient C (Female)

- received the dosages in Schedule C including direct injection into tumours (IT) in breast, including direct injection and intravenous administration (IV)
- surprisingly the tumours disappeared with no metastasis

EXAMPLE 4

Patient D (Female)

- received dosage amounts in Schedule D including direct injection(IT) into the tumours in the breast and intravenous (IV) administration
- patient held her own

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EXAMPLE 5

Patient E - aged 55 (Female) CA2122519

- carcinoma of the breast, treated with NSAIDs/HA and sodium ascorbate intravenously only (direct injections as well)
- has not metastasized from the position of tumour in the supraclavicular nodes over the past three years
- see Schedule E for dosages

EXAMPLE 6

Patient F - aged 73 (Female)

- carcinoma of the breast with liver metastases treated over 3 years with NSAIDs, HA, sodium ascorbate plus chemotherapy intravenously (IV);
- tumour was stable then began to grow but no metastases developed in this entire time (no injections appear to have been given into breast; however injections made into neck node left side)
- she discontinued treatment because of her age
- see Schedule F for dosages

EXAMPLE 7

Patient G - aged 56 (Female)

- carcinoma of the breast metastatic to supraclavicular nodes, disease has been stable for 4 years as a result of intermittent treatment with NSAIDs, sodium ascorbate and HA intravenously
- no direct injection
- see Schedule G for dosage amounts

EXAMPLE 8

Patient H - aged 81 (Female)

- carcinoma of the right lung with metastases to the mediastinum at diagnosis
- treated with weekly NSAIDs, sodium ascorbate, HA intravenously
- tumour remained stable without metastases and terminally some local growth
- treatment was discontinued as she was 81 years old, disabled and did not wish

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further therapy

- she died of cardiac failure

- see Schedule H for dosage amounts

EXAMPLE 9

Patient I - aged 64 (Male)

- carcinoma of the prostrate, remains entirely stable on NSAIDs/HA and sodium ascorbate given intravenously

- Schedule I sets out dosages

EXAMPLE 10

Patient J - aged 65 (Male)

- carcinoma of the colorectum metastatic to the liver, stable for 2 years without metastases

- treated one to two times per week with sodium ascorbate/HA and NSAIDs intravenously

- see Schedule J for dosage amounts

The following additional experimental data illustrates our results in the treatment of breast cancer patients. We have used by systemic administration, NSAIDs, sodium ascorbate and HA experimentally in these patients over a number of years. We have treated experimentally a total of 63 patients who had minimal surgery wherever possible. Patients received hormone blocking agents if they were positive for oestrogen or progesterone receptors. Only occasionally was an oophorectomy performed. We utilized low doses of chemotherapy, employing methotrexate (100 mg/100 mg HA on the first day) and 5-fluorouracil (5-FU) (350-500 mg/100 mg HA on the second and third days), initially without HA and subsequently with HA by injection. Where the tumour was considered more aggressive we used a four-drug combination in the injections (see Table 1).

TABLE I

Treatment for cancer of the breast

1. Surgery

   Modified radical mastectomy — 23 patients

   Segmental resection and lymph node dissection — 40 patients

2. Hormone manipulation

   Tamoxifen given — 33/63 patients

   Surgical oophorectomy — 3/63 patients

3. Chemotherapy

   Combination of MTX(mitoxantrone)+5-FU(5-FLUOROURACIL)

   or

   Combination of novantrone, 5-FU,

   mitomycin C, MTX (MITOXANTRONE)

4. Radiation

   One case

5. Hyperthermia

   EMW 915 MHz — Since 1982,

   to area of cancer — all patients

6. Immune modulation

   (a) Non-specific immune enhancement

   (b) Modification with PGE2 inhibitors high dose

   sodium ascorbate

Radiation was avoided. In these patients hyperthermia was employed by microwave technique to enhance the effect of the drugs. We have thus achieved a 90% survival for as long as nine years (see Table 2).

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TABLE 2

Cancer of the breast. Patients and survival

No. of patients:	63
Stage of disease:	I-14
	II-49
Age: Range	27-75
Mean	43 years
No. surviving free of cancer	55
Average survival time in years	8
No. surviving with disease	6
No. died of disease	2

It is apparent from these results that moderate doses of chemotherapy, adding NSAIDs and giving the drugs in HA, has resulted in an improved survival rate in a group of patients at high risk for recurrent disease.

An alternative experimental treatment for local breast cancer with or without systemic diseases was also devised. In one group of patients the initial four patients refused surgery and/or radiation. One had a recurrence in both breasts post-radiation; another post-radiation patient had skeletal metastases at the time of presentation. We injected mitoxantrone 1 mg in 10 mg HA from 1 to 6 times until the tumour disappeared. In addition, we gave systemic chemotherapy in HA and hyperthermia. Where appropriate, hormone-blocking drugs were used. Altogether 10 patients were treated in this fashion. All had a complete response in terms of regression of local disease (see Table 3).

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TABLE 3

Alternative experimental treatment of breast cancer

Patients

1. 10 patients treated experimentally over years
   4 recurrent after surgery
   1 recurrent post-irradiation
   - both breasts affected
2. 1/10 had distant metastases when diagnosed
   All had positive axillary lymph nodes

Results

- 10/10 complete local and regional node response
- 2/10 (initial patients) died of systemic disease
- 8/10 alive and well. Mean survival time=3 years
- Cosmetic result is excellent

The local reaction was not excessive although it consisted on initial enlargement of the area of the tumour site. What was impressive was the return of the breast to normal in some instances, and with only minimal scar tissue apparent on mammography in others.

This is a unique method of treatment. It appears that the drugs administered in HA affect almost exclusively the tumour tissue and do not produce a significant effect on normal tissue.

As many changes can be made to the dosage amounts used in the examples without departing from the scope of the inventions, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A method for the treatment of cancer in a human for the prevention/reduction of metastases in the human, said method comprising the steps of:

(1) directly injecting into the tumour a non-toxic dosage amount of a pharmaceutical composition comprising an effective non-toxic amount of an anti-cancer drug and/or drug suitable for use to treat cancer and an effective dosage amount of a form of hyaluronic acid, selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water, and

(2) administering systemically, a non-toxic dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and pharmaceutically acceptable salts thereof preferably sodium hyaluronate having a molecular weight less than 750,000 daltons

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)

(b) a chemotherapeutic agent

and combinations thereof optionally with

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(iii) an anti-oxidant.

2. The method of claim 1 wherein the frequency of treatment is one (1) to four (4) times monthly or more (as may be required).

3. The method of claim 1 wherein the form of cancer is breast cancer and the frequency of the direct injections into the malignant tumour in the breast and systemic administration is one (1) to three (3) times monthly or more (as may be required).

4. The method of claim 1, 2 or 3 wherein the administering systemically is by intravenous administration.

5. The treatment of claim 1, 2, or 3 further comprising treating the body with by hyperthermia.

6. A method for the treatment of cancer in a human for reducing metastasis in such human, said method comprising the steps of

(1) administering systemically to a human suffering from cancer, a dosage amount comprising an effective amount of a drug suitable for treating cancer alone, or preferably with an effective amount of a form of hyaluronic acid, selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts thereof, and combinations thereof, having a molecular weight of less than 750,000 daltons; and

(2) administering systemically a dosage amount of a pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid

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and pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)

(b) a chemotherapeutic agent

and combinations thereof

and optionally;

(iii) an anti-oxidant

7. The method of treatment of claim 6 wherein steps (1) and (2) are repeated as required.

8. A method of treatment for the reduction of the risk of a patient suffering from a cancer having the cancer metastasize (reduce the risk of such patient suffering from a metastasis or suffering from a metastatic effect), said method of treatment comprising

(1) administering systemically a dosage amount of a pharmaceutical composition comprising a drug in an effective non-toxic amount suitable for treating cancer alone or with an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons, and

(2) administering systemically a dosage amount of a

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pharmaceutically composition comprising: (i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and pharmaceutically acceptable salts thereof and combinations, having a molecular weight less than 750,000 daltons

(ii) a drug selected from

(a) a non-steroidal anti-inflammatory drug (NSAID) and

(b) a chemotherapeutic agent

and combinations thereof

optionally with

(iii) an anti-oxidant

said administration continuing at regular intervals over the period treatment is being given for treatment of cancer.

9. The method of treatment of claim 8 wherein method of treatment is administered about 1-4 times monthly.

10. A combination of dosage amounts of pharmaceutical composition comprising (1) in a form for systemic administration, a non-toxic dosage amount comprising

(i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and salts thereof pharmaceutically acceptable and combinations thereof, having a molecular weight

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less than 750,000 daltons, and

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID); and

(b) a chemotherapeutic agent

and combinations thereof and optionally (iii) an anti-oxidant and

(2) a non toxic effective dosage amount of a pharmaceutical composition for injection, said dosage amount being in injectable form and comprising an effective non-toxic amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons in sterile water.

11. The combination of claim 10 wherein the drug in dosage amount (1) is a NSAID.

12. The combination of claim 10 or 11 wherein the form of hyaluronic acid is sodium hyaluronate.

13. The use of effective non-toxic dosage amounts of pharmaceutical compositions, one said dosage amount comprising an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective dosage amount of a form of hyaluronic acid, selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water, suitable for injection and a second dosage amount of a

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pharmaceutical composition comprising

(i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons, and

(ii) a drug selected from

(a) a non-steroidal anti-inflammatory drug (NSAID) and

(b) a chemotherapeutic agent

and combinations thereof optionally with

(iii) an anti-oxidant

for (a) the treatment of cancer in a patient, (b) the prevention of metastasis in a patient suffering from cancer, and (c) the delivery of a drug to the lymph system and/or liver.

14. The use of each of

(I) a dosage amount of a pharmaceutical composition for systemic administration comprising an effective amount of a drug suitable for use to treat cancer alone in a suitable excipient or optionally with an effective amount of a form of hyaluronic acid selected from hyaluronic acid and/or pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons; and

(II) an effective dosage amount comprising

(i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid

and pharmaceutically acceptable salts thereof and combinations thereof, having a molecular weight less than 750,000 daltons, and

(ii) a drug selected from the group comprising

(a) a non-steroidal anti-inflammatory drug (NSAID)

(b) a chemotherapeutic agent

and combinations thereof

and optionally

(iii) an anti-oxidant for

(a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from cancer, and

(c) the delivery of a drug to the lymph system and/or liver.

15. The use of an effective non-toxic dosage amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective amount of a form of hyaluronic acid, selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water in the manufacture of a pharmaceutical composition for the prevention of metastases in a patient suffering from cancer.

16. The pharmaceutical composition of claim 16 in injectible form.

17. The use of (i) an effective dosage amount of a form of hyaluronic acid selected

from the group comprising hyaluronic acid and pharmaceutically acceptable salts thereof and combinations thereof having a molecular weight less than 750,000 daltons, and

(ii) a drug selected from (a) a non-steroidal anti-inflammatory drug (NSAID)

(b) a chemotherapeutic agent

and combinations thereof optionally with

(iii) an anti-oxidant in the manufacture of a pharmaceutical composition for the prevention of metastases in a patient suffering from cancer.

18. The use of claim 18 in a form for intravenous administration.

19. The use of

(I) an effective amount of an anti-cancer drug and/or a drug suitable for use to treat cancer and an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and/or pharmaceutically acceptable salts and combinations thereof, having a molecular weight less than 750,000 daltons in sterile water; and

(II) (i) an effective amount of a form of hyaluronic acid selected from the group comprising hyaluronic acid and pharmaceutically acceptable salts thereof and combinations

thereof having a molecular weight less than 750,000 daltons, and

(ii) a drug selected from

(a) a non-steroidal anti-inflammatory drug (NSAID); and

(b) a chemotherapeutic agent and combinations thereof optionally with

(iii) an anti-oxidant in the manufacture of two pharmaceutical compositions, composition (1) comprising the components of (I) and composition (2) comprising the components of (II) for

(a) the treatment of cancer in a patient,

(b) the prevention of metastasis in a patient suffering from cancer and

(c) the delivery of a drug to the lymph system and/or liver.